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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
[illegible]	
ART UNIT	**PAPER NUMBER**
[illegible]	5

DATE MAILED:
09/29/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/627,362	Melcher et al.
Examiner	**Art Unit**
Arun Chakrabarti	1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Feb 23, 2001 .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-21 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-21 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claims 1, the preamble of the instantly claimed method is drawn to a method of identifying redundant clones while the final process step is that of identifying clones for which the hybridization signal produced is different and it is thus unclear as to whether the instantly claimed methods are drawn to a method of identifying redundant clones or rather identifying clones for which the hybridization signal produced is different.

Claim 5 is rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claims 5, the preamble

of the instantly claimed method is drawn to a method of identifying previously characterized clones while the final process step is that of identifying clones for which the hybridization signal produced is different and it is thus unclear as to whether the instantly claimed methods are drawn to a method of identifying previously characterized or rather identifying clones for which the hybridization signal produced is different.

Claim 6 is rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claim 6, the preamble of the instantly claimed method is drawn to a method of making a normalized or subtracted cDNA library while the final process step is that of combining the first and second portions and it is thus unclear as to whether the instantly claimed methods are drawn to a method of making a normalized or subtracted cDNA library or rather combining the first and second portions

Method claim requires a last step or phrase in the last step that states the accomplishments of the goals for the method which were stated in the method's preamble.

Claims 1, 5 and 6 lack such a last step and are confusing because the additional method step is not sufficiently set forth. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashions. See Ex parte Erlich, 3 USPQ2d1011, p.1011 (Bd. Pat. Applicant. Int. 1986). It is suggested that an amended claim more clearly describing the intended steps be submitted.

3. Claims 15-21 are rejected over the recitation of the phrases, "related tissues or cells", "driver-tissue" and, "tester-tissue".

Regarding "related tissues or cells", it is not clear if the tissues or cells are physiologically related, or chemically related or biochemically related or obtained from the same individual or organism. The metes and bounds of the claims are vague and indefinite.

Regarding "driver-tissue", it is not clear if the tissue is driving some chemical or biological or biochemical pathway or the tissue is obtained from a driver of a vehicle. The metes and bounds of the claims are vague and indefinite.

Regarding "tester-tissue", it is not clear if the tissue is obtained from the person doing the experiment or any tissue being tested. It is also not clear how the "tester-tissue" is distinguished from "driver-tissue". The metes and bounds of the claims are vague and indefinite.

3. Claims 1-4 are rejected under 35 U.S.C. 112 (second paragraph) as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd.

App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1 recites the broad recitation of identifying redundant clones in a cDNA library, and the claim also recites identification of at least one redundant clone in a first portion of the library which is the narrower statement of the range/limitation.

Claims 1-14 are also rejected over the recitation of the phrase, "first portion of the cDNA library" and "first portion of the dscDNA" and "second portion of the dscDNA" . It is not clear how portion is defined and what portion of the library or dscDNA is claimed. It is also not clear how many portions constitute the cDNA library or dscDNA. Is the first single nucleotide of the library defined as first portion or first two nucleotides are considered as first portion or the last single nucleotide of the library or dscDNA defined as first portion or the last two nucleotides are considered as first portion or what? The metes and bounds of the claims are vague and indefinite.

Claim 5 is rejected in the absence of a step c). The metes and bounds of the claim is vague and indefinite.

Claims 10 and 16 are rejected over the use of improper Markush language "wherein the animal is". It is suggested to use the proper Markush language "wherein the animal is selected from the group consisting of".

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

5. Claims 1-5 are rejected under 35 U.S.C. 102 (e) as being anticipated by Somerville et al. (U.S. Patent 6,028,248) (February 22, 2000).

Somerville et al teach a method of identifying redundant clones in a cDNA library (Abstract and Column 17, line 25 to column 18, line 67).

a) identifying at least one redundant clone in a first portion of the cDNA (Column 18, lines 49-59 and Table 1 and Figures 1-3);

b) obtaining an isolated polynucleotide corresponding to the redundant clone (Column 18, lines 49-59 and Table 1 and Figures 1-3);

c) hybridizing a detectably labeled probe to an array of clones from the cDNA library, wherein the hybridizing is done in the presence and absence of the isolated polynucleotide obtained in (b) (Column 17, line 25 to column 18, line 67);

d) comparing the hybridization signal obtained for each arrayed clone in the presence and absence of the isolated polynucleotide (Column 17, line 25 to column 18, line 67 and Figures 1-3); and

e) identifying clones for which the hybridization signal produced is different in the presence and absence of the isolated polynucleotides as redundant clones (Figures 1-2 and Column 18, lines 60-67).

Somerville et al teach a method wherein the redundant clone is identified by comparing the sequences of at least 100 clones in the first portion of the cDNA library (Column 18, lines 60-67).

Somerville et al teach a method wherein the isolated polynucleotide in step (d) is detectably labeled and unlabeled (Column 18, lines 42-59).

Somerville et al teach a method of identifying previously characterized clones in a cDNA library (Abstract and Column 17, line 25 to column 18, line 67).

a) obtaining an isolated polynucleotide corresponding to previously identified clone (Column 18, lines 49-59 and Table 1 and Figures 1-3);

b) hybridizing a detectably labeled probe to an array of clones from the cDNA library, wherein the hybridizing is done in the presence and absence of the isolated polynucleotide obtained in (a) (Column 17, line 25 to column 18, line 67);

d) comparing the hybridization signal obtained for each arrayed clone in the presence and absence of the isolated polynucleotide (Column 17, line 25 to column 18, line 67 and Figures 1-3); and,

e) identifying clones for which the hybridization signal produced is different in the presence and absence of the isolated polynucleotides as previously characterized clones (Figures 1-2 and Column 18, lines 60-67).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 6-14 are rejected under 35 U.S.C. 103 (a) over Soares et al. (U.S. Patent 5,846,721) (December 8, 1998) in view of Makarov et al. (U.S. Patent 6,197,557 B1) (March 6, 2001).

Soares et al. teach an improved method of making a normalized or subtracted cDNA library (Abstract and Table 1) comprising :

a) obtaining double-stranded cDNA corresponding to mRNA from a human tissue (Table 1);

b) restricting a first portion of the double-stranded cDNA with a first restriction enzyme (Figure 2 and column 3, lines 49-54 and Column 2, lines 60-63 and Column 10, lines 38-42);

c) restricting a second portion of the double-stranded cDNA with a second nuclease or restriction enzyme (Column 2, lines 60-63 and Column 10, lines 38-42); the nuclease enzyme obviously serves the same purpose of restriction enzymes in this case, wherein restriction of double-stranded cDNA from the tissue with the first and second enzymes are predicted to produce restriction fragments (Figure 2 and column 3, lines 49-54).

Soares et al. teach the predicted average fragment size is determined by computer implemented inspection of gene sequences from Genbank (Column 17, line 60 to column 18, line 7).

Soares et al. do not teach the predicted average fragment sizes are within about 100-500 base pairs of each other.

However, it is *prima facie* obvious that selection of the specific number of base pairs in a restriction enzyme cleaved oligonucleotide fragment represents routine optimization with regard to sequence, length and compositions of starting double-stranded cDNA being cleaved and the nature of the restriction enzymes, which routine optimization parameters are explicitly recognized to an ordinary practitioner in the relevant art. As noted *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable

ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the restriction enzyme cleaved oligonucleotide fragment size selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Soares et al. teach the use of one restriction enzyme (column 3, lines 49-54).

Soares et al. do not teach the use of two restriction enzymes Dpn I and the second enzyme is Rsa I. in the same method.

Makarov et al. teach the method where the first enzyme is Dpn I and the second enzyme is Rsa I. (Column 13, lines 33-43 and Column 41, lines 51-58 and column 42, lines 45-56).

It would have been *further prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute within the method of Soares et al., the first enzyme is Dpn I and the second enzyme is Rsa I. of Makarov et al. since Makarov et al state, "Additionally, combinations of restriction enzymes, including those with four base recognition sequences, including, but not limited to, Tsp5091, Mae II, Dpn I, Rsa I, Taq I, and MseI, and those having "star activity", can be used in a restriction enzyme "cocktail" to produce essentially random nicks or breaks in a double-stranded nucleic acid (Column 41, lines 51-58)". By employing scientific reasoning and express motivation provided by Makarov et al., an ordinary artisan would have been motivated to combine and substitute within the method of Soares et al., the first enzyme is Dpn I and the second enzyme is Rsa I. of Makarov et al in order to improve

the method of making a normalized or subtracted cDNA library and also in order to achieve the express advantages, as noted by Makarov et al., of a restriction enzyme "cocktail" to produce essentially random nicks or breaks in a double-stranded nucleic acid which would naturally improve the method of making a normalized or subtracted cDNA library.

8. Claims 15-21 are rejected under 35 U.S.C. 103 (a) over Sutcliffe et al.(U.S. Patent 6,074,872) (June 13, 2000) in view of Soares et al. (U.S. Patent 5,846,721) (December 8, 1998).

Sutcliffe et al teach a method for selecting clones for analysis comprising (Examples, Column 37, line 15 to column 38, line 6):

a) preparing double-stranded cDNA corresponding to mRNA from each of a pair of related tissues, wherein one member of the pair is designated the driver-tissue and the other member of the pair is designated the tester-tissue (Examples, Column 37, lines 30-37);

b) using the double-stranded cDNA to prepare a driver-subtracted cDNA library and tester- subtracted cDNA library (Examples, Column 37, line 15 to column 38, line 6;

c) hybridizing clones from each of the libraries in (b) with detectably labeled cDNA probe corresponding to mRNA from one or both of the related tissues (Examples, Column 37, line 15 to column 38, line 6);

d) selecting low signal and high ratio clones with a desired signal intensity from the driver- subtracted cDNA library hybridized with cDNA probe from the driver tissue and the tester- subtracted cDNA library hybridized with cDNA probe from the tester tissue (Examples, Column 37, line 15 to column 38, line 6).

Sutcliffe et al teach a method wherein the tissues are from rat brain tissue (Examples, Column 37, lines 20-29).

Sutcliffe et al teach a method wherein the mRNA is from a pair of tissues related as diseased tissue and healthy tissue and the diseased tissue is from an animal model of a human disease (Examples, Column 37, lines 20-37).

Sutcliffe et al. inherently teach a method of comparing the quality of a two different subtracted cDNA libraries (Examples, Column 37, lines 20-57), comprising:

a) obtaining a first subtracted cDNA library and a second subtracted cDNA library, wherein each library is prepared from the same tester and driver RNAs (Examples, Column 37, lines 20-37);

b) preparing detectably labeled probe from DNA from each library (Examples, Column 37, lines 36-39);

c) hybridizing the probe from each library to an array of immobilized polynucleotides, wherein at least a plurality of the polynucleotides have the sequence of genes that are differently expressed in the tester RNA compared to the driver RNA, and detecting the hybridization of the probe to the immobilized polynucleotides.(Examples, Column 37, line 15 to column 38, line 6);

d) identifying at least one immobilized polynucleotide having a sequence that is differentially expressed in the tester RNA compared to the driver RNA and comparing the level of hybridization of probe from the first subtracted cDNA library to the polynucleotide with the level of hybridization of probe from the second subtracted cDNA library to the polynucleotide,

wherein the library having the higher level of hybridization of probe to the polynucleotide is identified as a higher quality library (Examples, Column 37, lines 37-49).

Sutcliffe et al do not teach a method of using normalized cDNA libraries from tissues.

Soares et al teach a method of using normalized cDNA libraries from tissues. (Figures 1A-1P and 2-4).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute within the method of Sutcliffe et al., the method of using normalized cDNA libraries from tissues of Soares et al. since Soares et al state, "For this reason, the use of normalized libraries, in which the frequency of all clones is within a narrow range has been shown to be advantageous for large scale sequencing (Column 1, lines 56-60)". By employing scientific reasoning and express motivation provided by Soares et al., an ordinary artisan would have been motivated to combine and substitute within the method of Sutcliffe et al., the method of using normalized cDNA libraries from tissues of Soares et al.. in order to achieve the express advantages, as noted by Soares et al., of the use of normalized libraries, in which the frequency of all clones is within a narrow range that has been shown to be advantageous for large scale sequencing.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph. D., whose telephone number is (703)

306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Arun Chakrabarti,

Patent Examiner,

June 14, 2001

JEFFREY FREDMAN
PRIMARY EXAMINER